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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/242,343	04/12/1999	DIRK VOLLENBROICH	2694-119P	9955

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BIRCH STEWART KOLASCH & BIRCH
PO BOX 747
FALLS CHURCH, VA 22040-0747

EXAMINER
BRUMBACK, BRENDA G

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 01/04/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/242,343	Applicant(s) VOLLENBROICH ET AL.	
	Examiner Brenda G. Brumback	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 November 2001* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-15,18 and 19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11, 13-15, 18, and 19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. This action is responsive to the amendment filed 11/01/2001. Claims 1, 18, and 19 were amended. Claims 1-11, 13-15, 18, and 19 are pending and under examination.

Claim Rejections - 35 USC § 103

2. The rejection of claims 1, 3-7, 9, 10, 14, 15, 18, and 19 under 35 U.S.C. 103(a) as being unpatentable over Itokawa et al.; the rejection of claims 1, 3, 9, and 10 under 35 U.S.C. 103(a) as being unpatentable over Naruse et al.; the rejection of claims 2 and 13 under 35 U.S.C. 103(a) as being unpatentable over either Itokawa et al. or Naruse et al. in view of Horowitz et al.; and the rejection of claims 8 and 11 under 35 U.S.C. 103(a) as being unpatentable over the combined teachings of Itokawa and Naruse in view of Vater et al. are all maintained for the reasons of record. Applicant's arguments have been fully considered but they are not persuasive for the following reasons.

Applicant argues that 1) there is no disclosure or suggestion in Itokawa et al. that by using the compounds of the presently claimed method all infectious particles in cell-free pharmaceutical products could be inactivated and 2) that an optimization of Itokawa et al. will not result in the full inactivation of viruses in pharmaceutical products while maintaining the activity of the products because Itokawa et al. nas nothing to do with inactivation, *i.e.* killing viruses in cell-free products. Applicant points to the XTT formazan assay referenced in Itokawa

et al. as measuring virus replication in cell culture rather than virus inactivation. Additionally, applicant argues that 3) there is no reasonable expectation of success for achieving a level of viral inactivation of $>10^4$ using only 1-100μM of the cyclic lipopeptide at room temperature within 30 minutes to 2 hours from the teachings of Itokawa et al.

Firstly, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the feature upon which applicant relies (i.e., full inactivation of all infectious particles) is not recited in the rejected claims. The claims recite a reduction in viral titer by a factor of $>10^4$. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Secondly, Itokawa et al. teach contacting a biological product with a cyclic lipopeptide at concentrations which overlap those of the claimed invention. Thus, the method described by Itokawa inherently produces the claimed result of reduction in viral titer by a factor of $>10^4$ without any need for optimization of concentrations. While Itokawa et al. is silent regarding the time of contact, absent some evidence to the contrary, the claimed time range is either inherent in the method described by Itokawa or constitutes routine optimization of a known test method. Applicant has provided no evidence to the contrary.

Regarding the XTT formazan assay and the Weislow et al. abstract, the *in vitro* cytopathic effects observed in cell culture are used as to measure inactivation of cell-free HIV-1, as well as to measure inactivation of HIV-1 in chronically infected cells (see the second sentence of the

abstract). The *in vitro* assay is used as a measure of viral infectivity after contact with a drug or an inactivating agent. This is equivalent to measuring virus inactivation. Applicant's arguments to the contrary are not supported in Weislow et al.

Lastly, in response to applicant's argument that there is no reasonable expectation of success based on the teachings found in Itokawa et al., the examiner maintains that the method of Itokawa et al. inherently produces the claimed results, *i.e.* contacting the biological product with 1-100μM of the cyclic lipopeptide achieves a level of viral inactivation of $>10^4$. Under the principles of inherency, if a prior art method, in its normal and usual operation, would necessarily perform the method claimed, then the method claimed will be considered to be anticipated by the prior art method. (MPEP 2112.02).

Regarding Naruse et al., the fact that Naruse et al. teaches assessing antiviral activity by measuring antiviral activity in an *in vitro* cell culture assay in no way teaches away from virus inactivation. Rather, as is taught also in the Weislow et al. abstract and discussed *supra*, assessment of viral infectivity in an *in vitro* cell culture assay is used as a measure of viral inactivation. There is no distinction in either Itokawa et al. or Naruse et al. between inhibition of viral replication and direct virus killing. Rather, virus inactivation is measured by both Itokawa et al. (as described in Weislow) and by Naruse. Furthermore, once again applicant is arguing a feature which is not claimed, as applicant's claims recite virus inactivation, not "direct virus killing".

In response to applicant's arguments regarding the "therapeutic index" and TD_{50}, it is noted that the present claims are not restricted to *in vivo* administration of the claimed compounds, but encompass inactivation of viruses in any cell-free biological product, including those intended for *in vitro* use.

Applicant argues that the method of Naruse et al. does not inherently anticipate the claimed method because "Naruse et al. does not use the compounds in the claimed method". This statement, however, is not understood, as Naruse et al. teaches the same compounds in the same concentrations as in the claimed method. Applicant has provided no evidence to the contrary.

Applicant arguments regarding direct viral inactivation and inhibition of viral replication have been addressed in a previous Office action and are again addressed herein at length *supra*. Applicant has not provided any evidence that the claimed method of virus inactivation is "a completely different means" than the method taught by Naruse et al., especially in light of the fact that Naruse et al. utilizes the very same compounds as those of the claimed invention.

- Claim Rejections - 35 USC § 112

3. The rejection of claims 1-9, 13-15, 18, and 19 under 35 U.S.C. 112, second paragraph, is maintained. Applicant's arguments have been fully considered but they are not persuasive.

Applicant's amendment of claim 1 to recite "viral titre reduced by a factor of $>10^4$" is noted; however, applicant's amendment does not overcome the rejection, as no units are recited.

As was pointed out in a previous Office action, without recitation of the unit of measurement, the recited value is indefinite. As has been previously suggested, applicant may overcome this rejection by amending the claim to recite either "ID_{50}/ml" or "$TCID_{50}$/ml".

Applicant's referral to the textbook, "Deutsches Arzneibuch" reference is noted; however, this reference was not found with the present amendment. Nevertheless, this portion of the rejection is withdrawn pursuant to applicant's amendment. "Room temperature" is understood to mean "15 to 25°C", as per applicant's statement filed with the amendment of 11/01/2001.

The rejection of claim 18 for recitation of "blood products" and "products from blood" and "biotechnological pharmaceutical products" is withdrawn pursuant to applicant's amendment thereof.

The rejection of claim 19 as being in improper Markush group form is withdrawn subsequent to applicant's amendment thereof.

4. The rejection of claims 1-10, 13-15, 18, and 19 under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inactivation of lipid-enveloped viruses in biological products intended for *in vitro* use, does not reasonably provide enablement for inactivation of lipid-enveloped viruses in pharmaceutical and blood products intended for *in vivo* administration is maintained. Applicant's arguments have been fully considered but they are not persuasive.

Applicant argues that the present rejection is not relevant because the claims are not drawn to administering the products *in vivo*. However, as was pointed out in the previous Office action, applicant's claims encompass any and all biological products, including vaccines and other pharmaceutical products for *in vivo* administration. Additionally, the portion of applicants disclosure at page 5 referenced in the amendment filed 11/01/2001, "as a result of the exceedingly low in vivo toxicity of the lipopeptides used according to the invention, these inactivating substances may also be allowed to remain in the pharmaceutical products at the above-mentioned concentrations" clearly indicates that the claimed method is intended to encompass treatment of pharmaceutical compositions intended for *in vivo* administration. Applicant has provided no argument or evidence to overcome the teachings of unpredictability which are found in the art and which were outlined in the previous Office action.

NEW GROUNDS OF REJECTION

Claim Rejections - 35 USC § 112

5. Claims 1-11, 13-15, 18, and 19 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Claim 1 has been amended to recite "a cell-free" biological product. While the specification provides support for the previously recited "non-cell culture biological products", there does not appear to be support for

a "cell-free" biological product, which differs in scope. This matter might be resolved if applicant were to point out where in the disclosure support for the newly recited material can be found.

Conclusion

6. No claims are allowed.

7. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brenda Brumback whose telephone number is (703) 306-3220. If the examiner can not be reached, inquiries can be directed to Supervisory Patent Examiner Anthony Caputa whose telephone number is (703) 308-3995. Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Examiner Brenda Brumback, Art Unit 1642 and should be marked "OFFICIAL" for entry into prosecution history or "DRAFT" for consideration by the examiner without entry. The Official FAX telephone number is (703) 872-9306 and the After Final FAX telephone number is (703) 872-9307. FAX machines will be available to receive transmissions 24 hours a day. In compliance with 1096 OG 30, the filing date accorded to each OFFICIAL fax transmission will be determined by the FAX machine's stamped date found on the last page of the transmission, unless that date is a Saturday, Sunday or Federal Holiday with the District of Columbia, in which case the OFFICIAL date of receipt will be the next business day.

Brenda Brumback
Patent Examiner